Massachusetts.
J Virol (UNITED STATES) Feb 1989, 63 (2) p759-68, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: AI24010, AI, NIAID; AI20530, AI, NIAID; AI19838, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Using nonsense and deletion mutants of herpes simplex virus type 1, we investigated the roles of three immediate-early proteins (ICP4, ICP27 and ICP0) in the establishment and reactivation of ganglionic latency in a mouse ocular model. DNA hybridization, superinfection-rescue, and cocultivation techniques provided quantitative data that distinguished between the failure of a virus to establish latency in the ganglion and its failure to reactivate. Null mutants with lesions in the genes for ICP4 and ICP27 did not replicate in the eye or in ganglia and failed to establish reactivatable latent infections. Three ICP0 deletion mutants which could replicate in the eye and ganglia varied in their ability to establish and reactivate from the latent state, demonstrating that ICP0 plays a role both in the establishment and the reactivation of latency. The use of viral mutants and a variety of stage-specific assays allowed us to better define the stages in the establishment and reactivation of herpes simplex virus

Possible inadvertent anticipation?

13/7/16
DIALOG(R)File 155:MEDLINE(R)

06947038 91303647
Divergent molecular pathways of productive and latent infection with a virulent strain of herpes simplex virus type 1.
Speck PG; Simmons A
Division of Medical Virology, Institute of Medical and Veterinary Science, Adelaide, Australia.
J Virol (UNITED STATES) Aug 1991, 65 (8) p4001-5, ISSN 0022-538X
Journal Code: KCV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Mutants of herpes simplex virus (HSV) have been used to show that a variety of key genes associated with initiation of lytic infection or replication of viral DNA are not essential for establishment of latency. These observations are extended in the present study, in which a virulent strain of HSV type 1 that is not compromised in its ability to productively infect neurons under favorable conditions was used to demonstrate early divergence of molecular pathways leading to productive and latent infection. Our experimental strategy made unique use of the segmental innervation of the vertebrate trunk to study the spread of virus throughout the peripheral nervous system after inoculation of mouse flanks. Evidence of viral gene expression, including that of immediate-early genes, was transient, confined to ganglia directly innervating the inoculated skin (8th through 12th thoracic segments), and seen only at sites from which infectious virus could be recovered. In contrast, neurons containing latency-associated transcripts and reactivatable virus were more widely distributed (sixth thoracic through first lumbar segments), from which we conclude that replication-competent HSV type 1 can establish latency without initiating productive infection.

13/7/17
DIALOG(R)File 155:MEDLINE(R)

06152247 88300879
Expression of herpes simplex virus type 1 (HSV-1) latency-associated transcripts and transcripts affected by the deletion in avirulent mutant HFEM: evidence for a new class of HSV-1 genes.
Spivack JG; Fraser NW
Wistar Institute, Philadelphia, Pennsylvania 19104.
J Virol (UNITED STATES) Sep 1988, 62 (9) p3281-7, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: AI-23968, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
During latent herpes simplex virus type 1 (HSV-1) infection in the trigeminal ganglia of mice, three virus-specific transcripts, 2.0, 1.5, and 1.45 kilobases (kb), are detectable by Northern (RNA) blot analysis, but only the 2.0-kb transcript can be detected in HSV-1-infected tissue culture cells (J.G. Spivack and N. W. Fraser, J. Virol. 61:3842-3847, 1987). Since these latency-associated genes map to a diploid region of the genome, transcription from the deletion mutant HFEM, which contains only one complete copy of these genes, was investigated to determine the effect of gene dosage. The 4.1-kb HFEM deletion is located between the alpha genes ICP0 and ICP27. ICP0 mRNA and the 2.0-kb latency-associated transcript were present at normal levels during HFEM infection, but ICP27 mRNA and 0.9- and 1.1-kb transcripts that map near the deletion were not readily detectable. The levels of expression of one or more of these genes might be an important determinant of HSV-1 virulence in animal hosts. ICP27 mRNA accumulated when protein synthesis was inhibited before HFEM infection, implying that the deletion may affect ICP27 regulatory rather than coding elements. Expression of the 2.0-kb latency-associated transcript was

characterized in infected CV-1 cells with metabolic inhibitors and strand-specific probes. On the basis of metabolic inhibitor studies, the gene encoding the 2.0-kb latency-associated transcript is not an alpha gene. During HSV-1 replication in infected tissue culture cells, the beta and gamma genes require the prior expression of alpha gene products. However, the latency-associated RNAs are expressed in the absence of detectable levels of alpha transcripts in latently infected mice. Thus, this latency-associated gene family appear to be regulated quite differently than alpha, beta, or gamma genes. For these reasons, and because the latency-associated genes may perform latent rather than replicative functions, we propose that they should be considered members of a new HSV-1 gene class, the lambda genes.

13/7/18
DIALOG(R)File 155:MEDLINE(R)

06135936 88036207
Herpes simplex virus type 1 oriL is not required for virus replication or for the establishment and reactivation of latent infection in mice.
Polvino-Bodnar M; Orberg PK; Schaffer PA
Laboratory of Tumor Virus Genetics, Dana-Farber Cancer Institute, Boston, Massachusetts.
J Virol (UNITED STATES) Nov 1987, 61 (11) p3528-35, ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: CA21082, CA, NCI; AI24010, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
During the course of experiments designed to isolate deletion mutants of herpes simplex virus type 1 in the gene encoding the major DNA-binding protein, ICP8, a mutant, d61, that grew efficiently in ICP8-expressing Vero cells but not in normal Vero cells was isolated (P. K. Orberg and P. A. Schaffer, J. Virol. 61:1136-1146, 1987). d61 was derived by cotransfection of ICP8-expressing Vero cells with infectious wild-type viral DNA and a plasmid, pDX, that contains an engineered 780-base-pair (bp) deletion in the ICP8 gene, as well as a spontaneous approximately 55-bp deletion in oriL. Gel electrophoresis and Southern blot analysis indicated that d61 DNA carried both deletions present in pDX. The ability of d61 to replicate despite the deletion in oriL suggested that a functional oriL is not essential for virus replication in vitro. Because d61 harbored two mutations, a second mutant, ts+7, with a deletion in oriL-associated sequences and an intact ICP8 gene was constructed. Both d61 and ts+7 replicated efficiently in their respective permissive host cells, although their yields were slightly lower than those of control viruses with intact oriL sequences. An in vitro test of origin function of isolated oriL sequences from wild-type virus and ts+7 showed that wild-type oriL, but not ts+7 oriL, was functional upon infection with helper virus. In an effort to determine the requirement for oriL in latency, ts+7 was compared with wild-type virus for its ability to establish, maintain, and be reactivated from latent infection in a murine eye model. The mutant was reactivated as efficiently as was wild-type virus from trigeminal ganglia after cocultivation with permissive cells, and each of the seven reactivated isolates was shown to carry the approximately 150-bp deletion characteristic of ts+7. These observations demonstrate that oriL is not required for virus replication in vitro or for the establishment and reactivation of latent infection in vivo.

13/7/19
DIALOG(R)File 155:MEDLINE(R)

05806096 89095004
Immediate-early regulatory gene mutants define different stages in the establishment and reactivation of herpes simplex virus latency.
Leib DA; Coen DM; Bogard CL; Hicks KA; Yager DR; Knipe DM; Tyler KL; Schaffer PA
Laboratory of Tumor Virus Genetics, Dana-Farber Cancer Institute, Boston,

FILE 'USPAT' ENTERED AT 14:42:51 ON 05 OCT 1998
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* WELCOME TO THE *
* U.S. PATENT TEXT FILE *
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15 ICP27
1857 ICP
837119 27
2 ICP 27
(ICP(W)27)
L1 16 ICP27 OR ICP 27
=> s icp8 or icp 8
11 ICP8
1857 ICP
1876258 8
2 ICP 8
(ICP(W)8)
L2 13 ICP8 OR ICP 8
=> d l1 1-16

1. 5,804,413, Sep. 8, 1998, Herpes simplex virus strains for gene transfer; Neal A. DeLuca, 435/69.1, 235.1, 320.1, 364 [IMAGE AVAILABLE]

2. 5,795,778, Aug. 18, 1998, Method and reagent for inhibiting herpes simplex virus replication; Kenneth G. Draper, 435/326, 236, 320.1; 514/44; 536/23.1 [IMAGE AVAILABLE]

3. 5,795,721, Aug. 18, 1998, High affinity nucleic acid ligands of ICP4; Ross S. Rabin, et al., 435/6, 91.1, 91.2; 436/501; 536/23.1 [IMAGE AVAILABLE]

4. 5,776,468, Jul. 7, 1998, Vaccine compositions containing 3-0 deacylated monophosphoryl lipid A; Pierre Hauser, et al., 424/226.1, 192.1, 202.1, 282.1 [IMAGE AVAILABLE]

5. 5,750,398, May 12, 1998, Vector, element and method for inhibiting immune recognition; David C. Johnson, et al., 435/375; 424/199.1; 435/69.1, 91.1, 320.1, 325, 377, 465; 514/44 [IMAGE AVAILABLE]

6. 5,750,110, May 12, 1998, Vaccine composition containing adjuvants; John Paul Prieels, et al., 424/208.1, 184.1, 188.1, 204.1 [IMAGE AVAILABLE]

7. 5,728,379, Mar. 17, 1998, Tumor- or cell-specific herpes simplex virus replication; Robert L. Martuza, et al., 424/93.2; 435/320.1, 456 [IMAGE AVAILABLE]

8. 5,698,431, Dec. 16, 1997, Herpes simplex virus mutant UL41NHB; David A. Leib, 435/236, 235.1, 948 [IMAGE AVAILABLE]

9. 5,658,724, Aug. 19, 1997, Herpes simplex virus strains deficient for the essential immediate early genes ICP4 and **ICP27** and methods for their production, growth and use; Neal A. DeLuca, 435/5, 235.1, 236, 320.1, 325, 364, 465 [IMAGE AVAILABLE]

10. 5,580,564, Dec. 3, 1996, Method for modifying the cell, tissue or host tropism of microorganisms; recombinant microorganisms obtained in this way and use thereof in medicine and veterinary medicine; Koenraad L. Glazenburg, et al., 424/229.1, 815; 435/236; 536/23.1, 24.1 [IMAGE AVAILABLE]

11. 5,525,468, Jun. 11, 1996, Assay for Ribozyme target site; James A. McSwiggen, 435/6, 91.2; 536/25.1 [IMAGE AVAILABLE]

12. 5,496,698, Mar. 5, 1996, Method of isolating ribozyme targets; Kenneth G. Draper, et al., 435/6, 91.31, 320.1; 514/44; 536/23.1, 23.2, 24.5 [IMAGE AVAILABLE]

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14. 5,352,596, Oct. 4, 1994, Pseudorabies virus deletion mutants involving the EPO and LLT genes; Andrew K. Cheung, et al., 424/205.1, 229.1, 815; 435/235.1, 236, 456, 463, 948 [IMAGE AVAILABLE]

15. 5,334,498, Aug. 2, 1994, Herpes simplex virus 1 UL13 gene product: methods and compositions; Bernard Roizman, et al., 435/5, 183, 188, 194 [IMAGE AVAILABLE]

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=> d l2 1-13

1. 5,807,978, Sep. 15, 1998, Immunogenic peptides of prostate specific antigen; William J. Kokolus, et al., 530/300; 424/184.1, 185.1, 277.1; 530/326, 327, 403 [IMAGE AVAILABLE]

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3. 5,763,178, Jun. 9, 1998, Oscillating signal amplifier for nucleic acid detection; Jack G. Chirikjian, et al., 435/6; 536/23.1, 24.3 [IMAGE AVAILABLE]

4. 5,728,379, Mar. 17, 1998, Tumor- or cell-specific herpes simplex virus replication; Robert L. Martuza, et al., 424/93.2; 435/320.1, 456 [IMAGE AVAILABLE]

5. 5,665,873, Sep. 9, 1997, Glucocorticoid response elements; Priscilla A. Schaffer, et al., 536/24.1, 23.1 [IMAGE AVAILABLE]

6. 5,616,461, Apr. 1, 1997, Assay for antiviral activity using complex of herpesvirus origin of replication and cellular protein; Priscilla A. Schaffer, et al., 435/6, 5, 32; 436/501 [IMAGE AVAILABLE]

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8. 5,603,726, Feb. 18, 1997, Multichannel cochlear implant system including wearable speech processor; Joseph H. Schulman, et al., 607/57 [IMAGE AVAILABLE]

9. 5,569,307, Oct. 29, 1996, Implantable cochlear stimulator having backtelemetry handshake signal; Joseph H. Schulman, et al., 607/56, 55, 57, 60 [IMAGE AVAILABLE]

10. 5,531,774, Jul. 2, 1996, Multichannel implantable cochlear stimulator having programmable bipolar, monopolar or multipolar electrode configurations; Joseph H. Schulman, et al., 607/56, 55, 57 [IMAGE AVAILABLE]

11. 5,522,865, Jun. 4, 1996, Voltage/current control system for a human tissue stimulator; Joseph H. Schulman, et al., 607/56, 32, 55, 57, 60 [IMAGE AVAILABLE]

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13. 4,572,896, Feb. 25, 1986, Monoclonal antibodies to herpes simplex virus type I polypeptides; Berge Hampar, et al., 435/6, 70.21, 339, 452, 948; 436/548; 530/350, 388.3, 395 [IMAGE AVAILABLE]

=> s ie63 or vmw63 or ie2 or ul54
2 IE63
1 VMW63
111 IE2
3 UL54
L3 113 IE63 OR VMW63 OR IE2 OR UL54
=> s herpes? and l3
5883 HERPES?
L4 12 HERPES? AND L3
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1. 5,801,235, Sep. 1, 1998, Oligonucleotides with anti-cytomegalovirus activity; Gregory S. Pari, 536/24.5; 435/6, 375; 536/24.3, 24.33 [IMAGE AVAILABLE]

2. 5,795,778, Aug. 18, 1998, Method and reagent for inhibiting **herpes** simplex virus replication; Kenneth G. Draper, 435/326, 236, 320.1; 514/44; 536/23.1 [IMAGE AVAILABLE]

3. 5,789,573, Aug. 4, 1998, Antisense inhibition of ICAM-1, E-selectin, and CMV IE1/**IE2**; Brenda Baker, et al., 536/24.5; 435/6, 91.1; 536/23.1, 24.31, 24.33 [IMAGE AVAILABLE]

4. 5,783,383, Jul. 21, 1998, Method of detecting cytomegalovirus (CMV); Kazuhiro Kondo, et al., 435/5; 204/456; 435/6, 7.1, 91.1, 91.2; 530/300, 350, 388.1 [IMAGE AVAILABLE]

5. 5,767,102, Jun. 16, 1998, Antisense composition and method for treatment of CMV infection; Kenneth G. Draper, et al., 514/44; 435/6, 91.1; 536/23.1, 24.3, 24.5 [IMAGE AVAILABLE]

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7. 5,728,379, Mar. 17, 1998, Tumor- or cell-specific **herpes** simplex virus replication; Robert L. Martuza, et al., 424/93.2; 435/320.1, 456 [IMAGE AVAILABLE]

8. 5,595,978, Jan. 21, 1997, Composition and method for treatment of CMV retinites; Kenneth G. Draper, et al., 514/44; 435/6, 91.1; 536/23.1, 24.5 [IMAGE AVAILABLE]

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12. 5,180,813, Jan. 19, 1993, Early envelope glycoprotein of human cytomegalovirus (HMCV) and monoclonal antibodies to the glycoproteins; Mark F. Stinski, 530/388.3; 424/147.1, 230.1; 435/70.21; 530/389.4, 395; 536/23.72 [IMAGE AVAILABLE]

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File 155:MEDLINE(R)  1966-1998/Nov W3
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          19  S6
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      340353  S8
    S9      2  S7 AND S8
? t s9/6/1 2

 9/6/1
08764374   96422673
 Induction of protective immunity against herpes simplex virus with DNA
encoding the immediate early protein ICP 27.
1995

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07859777   94118416
 Immunization with replication-defective mutants of herpes simplex virus
type 1: sites of immune intervention in pathogenesis of challenge virus
infection.
Feb 1994
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       177184  MUTAT?
    S10 221336  MUTANT? OR MUTAT?
? s s7 and s10
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      221336  S10
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Set    Items  Description
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S3       158  ICP8 OR ICP(W)8
S4        51  IE63 OR VMW63 OR UL54
S5        31  IE2 AND HERPES?
S6        19  ALPHA(W)27 AND HERPES?
S7       366  S1 OR S3 OR S4 OR S5 OR S6
S8    340353  INJECT?
S9         2  S7 AND S8
S10   221336  MUTANT? OR MUTAT?
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S11 149 S7 AND S10
? t s11/7/125 145

11/7/125
DIALOG(R)File 155:MEDLINE(R)

06122617 87141331
Expression of herpes simplex virus type 1 major DNA-binding protein, ICP8, in transformed cell lines: complementation of deletion mutants and inhibition of wild-type virus.
Orberg PK; Schaffer PA
J Virol (UNITED STATES) Apr 1987, 61 (4) p1136-46, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: CA-21082, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To minimize the contribution of residual activity associated with the temperature-sensitive (ts) form of ICP8 specified by available ts mutants, deletion mutations in this gene were constructed. Cells permissive for the generation and propagation of ICP8 deletion mutants were first obtained. Vero cells were cotransfected with pKEF-P4, which contains the gene for ICP8, and pSV2neo or a hybrid plasmid containing the G418 resistance gene linked to pKEF-P4. Of the 48 G418-resistant cell lines, 21 complemented ICP8 ts mutants in plaque assays at the nonpermissive temperature. Four of these were examined by Southern blot analysis and shown to contain 1 to 3 copies of the ICP8 gene per haploid genome equivalent. Cell line U-47 was used as the permissive host for construction of ICP8 deletion mutants. In addition to cell lines which complemented ts mutants, two lines, U-27 and U-35, significantly inhibited plaque formation by wild-type virus, contained 30 and 100 copies of the ICP8 gene per haploid genome equivalent, respectively, and expressed large amounts of ICP8 after infection with wild-type virus. At low but not high multiplicities of infection, this inhibition was accompanied by underproduction of viral polypeptides of the early, delayed-early, and late kinetic classes. For construction of deletion mutants, a 780-base-pair XhoI fragment was deleted from pSG18-SalIA, a plasmid which contains the gene for ICP8, to yield pDX. U-47 cells were then cotransfected with pDX and infectious wild-type DNA. Mutant d61, isolated from the progeny of cotransfection, was found to contain both the engineered deletion in the ICP8 gene and an oriL-associated deletion of approximately 55 base pairs. Because d61 contained two mutations, a second mutant, d21, which carried the engineered ICP8 deletion but an intact oriL, was constructed by cotransfection of U-47 cells with wild-type DNA and an SalI-KpnI fragment purified from pDX. Phenotypic analysis of d21 and d61 revealed that they were similar in all properties examined: both exhibited efficient growth in U-47 cells but not in Vero cells; both induced the synthesis of an ICP8 polypeptide which was smaller than the wild-type form of the protein and which, unlike the wild-type protein, was found in the cytoplasm and not the nucleus of infected Vero cells; and nonpermissive Vero cells infected with either mutant failed to express late viral polypeptides.

11/7/145
DIALOG(R)File 155:MEDLINE(R)

05805781 89068829
Herpes simplex virus type 1 ICP27 deletion mutants exhibit altered patterns of transcription and are DNA deficient.
McCarthy AM; McMahan L; Schaffer PA
Laboratory of Tumor Virus Genetics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115.
J Virol (UNITED STATES) Jan 1989, 63 (1) p18-27, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: CA20260, CA, NCI; AI24010, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Infected cell polypeptide 27 (ICP27, alpha 27, IE63) is the 63-kilodalton product of an immediate-early gene of herpes simplex virus. Functional analysis of temperature-sensitive mutants in herpes simplex virus type 1 ICP27 demonstrated that this protein plays an essential role in virus replication (W. R. Sacks, C. C. Greene, D. P. Aschman, and P. A. Schaffer, J. Virol. 55:796-805, 1985). Because the temperature-sensitive forms of ICP27 induced by the mutants affected gene expression to differing degrees, these mutants were not suitable for establishing the ICP27 null phenotype. For this purpose we generated deletion mutants in ICP27--3dl1.2 and 5dl1.2--lacking the transcriptional start site as well as portions of the promoter and coding sequences of the gene. These mutants failed to specify ICP27-specific transcripts and proteins and were replication incompetent. The mutants induced the synthesis of greatly reduced levels of viral DNA (18% of wild-type levels) and were characterized by the overexpression of early proteins, reduced levels of gamma 1 proteins, and the absence of detectable gamma 2 proteins. The alterations in viral protein synthesis appeared to occur at the level of transcription. The phenotypic properties of the mutants were consistent with the results of transient expression assays demonstrating that ICP27 acts to down-regulate transcription of early genes and to further up-regulate transcription of late genes whose expression is induced by ICP0 and ICP4. Because ICP27 is not thought to be directly involved in viral DNA synthesis, it is likely that the reduced levels of viral DNA characteristic of deletion mutant-infected cells is a consequence of aberrant regulation of certain early genes whose products are involved in viral DNA synthesis and late genes whose products are required to stabilize viral DNA once synthesized. Taken together, these findings suggest an essential role for ICP27 in the modulation of early and late gene expression at the transcriptional level.
? s mouse or mice

175884 MOUSE
507693 MICE
S12 528122 MOUSE OR MICE
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Set Items Description
S1 143 ICP27 OR ICP(W)27
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S3 158 ICP8 OR ICP(W)8
S4 51 IE63 OR VMW63 OR UL54
S5 31 IE2 AND HERPES?
S6 19 ALPHA(W)27 AND HERPES?
S7 366 S1 OR S3 OR S4 OR S5 OR S6
S8 340353 INJECT?
S9 2 S7 AND S8
S10 221336 MUTANT? OR MUTAT?
S11 149 S7 AND S10
S12 528122 MOUSE OR MICE
? s s11 and s12
149 S11
528122 S12
S13 19 S11 AND S12
? t s13/7/15-19

13/7/15
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07300175 93059652
Replication-defective mutants of herpes simplex virus (HSV) induce cellular immunity and protect against lethal HSV infection.
Nguyen LH; Knipe DM; Finberg RW
Laboratory of Infectious Diseases, Dana-Farber Cancer Institute, Boston, Massachusetts.
J Virol (UNITED STATES) Dec 1992, 66 (12) p7067-72, ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: CA26345, CA, NCI; AI20530, AI, NIAID; AI20382, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Live viruses and live virus vaccines induce cellular immunity more readily than do inactivated viruses or purified proteins, but the mechanism by which this process occurs is unknown. A trivial explanation would relate to the ability of live viruses to spread and infect more cells than can inactivated virus. We have used live but replication-defective mutants to investigate this question. Our studies indicate that the immune responses of mice to live virus differ greatly from the responses to inactivated virus even when the virus does not complete a replicative cycle. Further, these studies indicate that herpes simplex virus-specific T-cell responses can be generated by infection with replication-defective mutant viruses. These data indicate that the magnitude of the cellular immunity to herpes simplex virus may be proportional to the number or quantity of different viral gene products expressed by an immunizing virus.

13/7/16
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06947038 91303647
Divergent molecular pathways of productive and latent infection with a virulent strain of herpes simplex virus type 1.
Speck PG; Simmons A
Division of Medical Virology, Institute of Medical and Veterinary Science, Adelaide, Australia.
J Virol (UNITED STATES) Aug 1991, 65 (8) p4001-5, ISSN 0022-538X Journal Code: KCV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Mutants of herpes simplex virus (HSV) have been used to show that a variety of key genes associated with initiation of lytic infection or replication of viral DNA are not essential for establishment of latency. These observations are extended in the present study, in which a virulent strain of HSV type 1 that is not compromised in its ability to productively infect neurons under favorable conditions was used to demonstrate early divergence of molecular pathways leading to productive and latent infection. Our experimental strategy made unique use of the segmental innervation of the vertebrate trunk to study the spread of virus throughout the peripheral nervous system after inoculation of mouse flanks. Evidence of viral gene expression, including that of immediate-early genes, was transient, confined to ganglia directly innervating the inoculated skin (8th through 12th thoracic segments), and seen only at sites from which infectious virus could be recovered. In contrast, neurons containing latency-associated transcripts and reactivatable virus were more widely distributed (sixth thoracic through first lumbar segments), from which we conclude that replication-competent HSV type 1 can establish latency without initiating productive infection.

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06152247 88300879
Expression of herpes simplex virus type 1 (HSV-1) latency-associated transcripts and transcripts affected by the deletion in avirulent mutant HFEM: evidence for a new class of HSV-1 genes.
Spivack JG; Fraser NW
Wistar Institute, Philadelphia, Pennsylvania 19104.

J Virol (UNITED STATES) Sep 1988, 62 (9) p3281-7, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: AI-23968, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

During latent herpes simplex virus type 1 (HSV-1) infection in the trigeminal ganglia of mice, three virus-specific transcripts, 2.0, 1.5, and 1.45 kilobases (kb), are detectable by Northern (RNA) blot analysis, but only the 2.0-kb transcript can be detected in HSV-1-infected tissue culture cells (J.G. Spivack and N. W. Fraser, J. Virol. 61:3842-3847, 1987). Since these latency-associated genes map to a diploid region of the genome, transcription from the deletion mutant HFEM, which contains only one complete copy of these genes, was investigated to determine the effect of gene dosage. The 4.1-kb HFEM deletion is located between the alpha genes ICP0 and ICP27. ICP0 mRNA and the 2.0-kb latency-associated transcript were present at normal levels during HFEM infection, but ICP27 mRNA and 0.9- and 1.1-kb transcripts that map near the deletion were not readily detectable. The levels of expression of one or more of these genes might be an important determinant of HSV-1 virulence in animal hosts. ICP27 mRNA accumulated when protein synthesis was inhibited before HFEM infection, implying that the deletion may affect ICP27 regulatory rather than coding elements. Expression of the 2.0-kb latency-associated transcript was characterized in infected CV-1 cells with metabolic inhibitors and strand-specific probes. On the basis of metabolic inhibitor studies, the gene encoding the 2.0-kb latency-associated transcript is not an alpha gene. During HSV-1 replication in infected tissue culture cells, the beta and gamma genes require the prior expression of alpha gene products. However, the latency-associated RNAs are expressed in the absence of detectable levels of alpha transcripts in latently infected mice. Thus, this latency-associated gene family appear to be regulated quite differently than alpha, beta, or gamma genes. For these reasons, and because the latency-associated genes may perform latent rather than replicative functions, we propose that they should be considered members of a new HSV-1 gene class, the lambda genes.

13/7/18
DIALOG(R)File 155:MEDLINE(R)

06135936 88036207

Herpes simplex virus type 1 oriL is not required for virus replication or for the establishment and reactivation of latent infection in mice.

Polvino-Bodnar M; Orberg PK; Schaffer PA
Laboratory of Tumor Virus Genetics, Dana-Farber Cancer Institute, Boston, Massachusetts.

J Virol (UNITED STATES) Nov 1987, 61 (11) p3528-35, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: CA21082, CA, NCI; AI24010, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

During the course of experiments designed to isolate deletion mutants of herpes simplex virus type 1 in the gene encoding the major DNA-binding protein, ICP8, a mutant, d61, that grew efficiently in ICP8-expressing Vero cells but not in normal Vero cells was isolated (P. K. Orberg and P. A. Schaffer, J. Virol. 61:1136-1146, 1987). d61 was derived by cotransfection of ICP8-expressing Vero cells with infectious wild-type viral DNA and a plasmid, pDX, that contains an engineered 780-base-pair (bp) deletion in the ICP8 gene, as well as a spontaneous approximately 55-bp deletion in oriL. Gel electrophoresis and Southern blot analysis indicated that d61 DNA carried both deletions present in pDX. The ability of d61 to replicate despite the deletion in oriL suggested that a functional oriL is not essential for virus replication in vitro. Because d61 harbored two mutations, a second mutant, ts+7, with a deletion in oriL-associated sequences and an intact ICP8 gene was constructed. Both d61 and ts+7 replicated efficiently in their respective permissive host cells, although their yields were slightly lower than those of control viruses with intact oriL sequences. An in vitro test of origin function of isolated oriL sequences from wild-type virus and ts+7 showed that wild-type oriL, but not ts+7 oriL, was functional upon infection with helper virus. In an effort to determine the requirement for oriL in latency, ts+7 was compared with wild-type virus for its ability to establish, maintain, and be reactivated from latent infection in a murine eye model. The mutant was reactivated as efficiently as was wild-type virus from trigeminal ganglia after cocultivation with permissive cells, and each of the seven reactivated isolates was shown to carry the approximately 150-bp deletion characteristic of ts+7. These observations demonstrate that oriL is not required for virus replication in vitro or for the establishment and reactivation of latent infection in vivo.

13/7/19
DIALOG(R)File 155:MEDLINE(R)

05806096 89095004

Immediate-early regulatory gene mutants define different stages in the establishment and reactivation of herpes simplex virus latency.

Leib DA; Coen DM; Bogard CL; Hicks KA; Yager DR; Knipe DM; Tyler KL; Schaffer PA
Laboratory of Tumor Virus Genetics, Dana-Farber Cancer Institute, Boston, Massachusetts.

J Virol (UNITED STATES) Feb 1989, 63 (2) p759-68, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: AI24010, AI, NIAID; AI20530, AI, NIAID; AI19838, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Using nonsense and deletion mutants of herpes simplex virus type 1, we investigated the roles of three immediate-early proteins (ICP4, ICP27 and ICP0) in the establishment and reactivation of ganglionic latency in a mouse ocular model. DNA hybridization, superinfection-rescue, and cocultivation techniques provided quantitative data that distinguished between the failure of a virus to establish latency in the ganglion and its failure to reactivate. Null mutants with lesions in the genes for ICP4 and ICP27 did not replicate in the eye or in ganglia and failed to establish reactivatable latent infections. Three ICP0 deletion mutants which could replicate in the eye and ganglia varied in their ability to establish and reactivate from the latent state, demonstrating that ICP0 plays a role both in the establishment and the reactivation of latency. The use of viral mutants and a variety of stage-specific assays allowed us to better define the stages in the establishment and reactivation of herpes simplex virus type 1 latency.
? ds

Set	Items	Description
S1	143	ICP27 OR ICP(W)27
S2	0	ICP8 O ICP(W)8
S3	158	ICP8 OR ICP(W)8
S4	51	IE63 OR VMW63 OR UL54
S5	31	IE2 AND HERPES?
S6	19	ALPHA(W)27 AND HERPES?
S7	366	S1 OR S3 OR S4 OR S5 OR S6
S8	340353	INJECT?
S9	2	S7 AND S8
S10	221336	MUTANT? OR MUTAT?
S11	149	S7 AND S10
S12	528122	MOUSE OR MICE
S13	19	S11 AND S12

? t s13/7/12

13/7/12
DIALOG(R)File 155:MEDLINE(R)

07858416 94110602
Mechanism of virus-induced Ig subclass shifts.
Nguyen L; Knipe DM; Finberg RW
Laboratory of Infectious Diseases, Dana-Farber Cancer Institute, Boston, MA 02115.
J Immunol (UNITED STATES) Jan 15 1994, 152 (2) p478-84, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI20381, AI, NIAID; AI24010, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Infection of mice with live viruses leads to a dramatic increase in the amount of IgG2a Ig with a consequent shift in the ratio of IgG1/IgG2a. To examine the Ig subclass shift induced by viral infection, we challenged mice with live virus, inactivated virus, or replication-defective mutant viruses that were able to infect cells and produce some viral proteins but were not able to complete a replicative cycle. While killed (or inactivated) virus was capable of inducing HSV-specific antibody, it did not stimulate a shift in the subclass of the total Ig. Replication-defective mutant viruses that fail to express a functional ICP8 or ICP27 protein, but not a mutant expressing a defective ICP4 protein, were able to stimulate the shift. Thus, only a portion of the lytic cycle is sufficient to induce the shift. At least part of the effect is mediated by IFN-gamma.
? t s13/7/9-11

13/7/9
DIALOG(R)File 155:MEDLINE(R)

08611784 96251937
Mechanisms of immunization with a replication-defective mutant of herpes simplex virus 1.
Morrison LA; Knipe DM
Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA.
Virology (UNITED STATES) Jun 15 1996, 220 (2) p402-13, ISSN 0042-6822 Journal Code: XEA
Contract/Grant No.: AI 20410, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have investigated the mechanisms by which subcutaneous immunization of mice with a replication-defective mutant of herpes simplex virus 1 protects against infection of the eye and latent infection of the trigeminal ganglion following corneal challenge. First, we have shown that immunization reduces the number of trigeminal ganglion neurons in challenged animals that express the latency-associated transcript. This indicates that the reduction in the incidence of latent infection by challenge virus is likely due to immune mechanisms and not saturation of the potential sites of latent infection by the immunizing mutant virus itself. Second, the duration of protective immunity against acute infection, keratitis, and latent infection was similar in mice immunized with replication-defective or -competent virus; thus, the replication-defective mutant virus is able to induce durable immunity apparently without spread in the host. Third, although the mutant virus showed no evidence of replication in vivo, it was present in footpad tissue in an infectious form for several days. This surprising observation raises the possibility that continued infection events by input virus over an extended period of time may have a boosting effect on the developing immune response which could explain, at least in part, the capacity of these

replication-defective mutant viruses to elicit a robust and durable immunity despite their inability to spread within the host.

13/7/10
DIALOG(R)File 155:MEDLINE(R)
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08104411 95126771
A herpes simplex virus type 1 ICP22 deletion mutant is altered for virulence and latency in vivo.
Poffenberger KL; Idowu AD; Fraser-Smith EB; Raichlen PE; Herman RC
Syntex Research, Palo Alto, California.
Arch Virol (AUSTRIA) 1994, 139 (1-2) p111-9, ISSN 0304-8608
Journal Code: 8L7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The in vivo function of the herpes simplex virus type 1 immediate early gene ICP22 has been investigated in mice and guinea pigs using a deletion mutant (del22Z) of HSV-1(F) that lacks all but 18 nucleotides of the ICP22 coding sequence. This mutant carries the bacterial lacZ gene at the site of the deletion and makes functional beta-galactosidase, but is unable to synthesize any detectable ICP22 messenger RNA or protein in vitro. Del22Z was impaired in its ability to cause death in mice following intracerebral, intraperitoneal, or intravaginal inoculation. The mutant failed to produce lesions or other visible signs of infection after bilateral corneal infection of mice but could be recovered from trigeminal ganglia explanted at day 30 after inoculation. Del22Z replicated poorly after intravaginal inoculation of mice and guinea pigs in comparison to the parental virus, and was not recoverable from the dorsal root ganglia of either species. Nevertheless, del22Z sequences could be detected in the dorsal root ganglia of guinea pigs at day 30 by the polymerase chain reaction. These studies demonstrate that the ICP22 gene product is required for acute infection and virulence in two standard in vivo animal models.

13/7/11
DIALOG(R)File 155:MEDLINE(R)
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07859777 94118416
Immunization with replication-defective mutants of herpes simplex virus type 1: sites of immune intervention in pathogenesis of challenge virus infection.
Morrison LA; Knipe DM
Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, Massachusetts 02115.
J Virol (UNITED STATES) Feb 1994, 68 (2) p689-96, ISSN 0022-538X
Journal Code: KCV
Contract/Grant No.: PO1 AI 24010, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Replication-defective mutants of herpes simplex virus type 1 (HSV-1) were used as a new means to immunize mice against HSV-1-mediated ocular infection and disease. The effects of the induced immune responses on pathogenesis of acute and latent infection by challenge virus were investigated after corneal inoculation of immunized mice with virulent HSV-1. A single subcutaneous injection of replication-defective mutant virus protected mice against development of encephalitis and keratitis. Replication of the challenge virus at the initial site of infection was lower in mice immunized with attenuated, wild-type parental virus (KOS1.1) or replication-defective mutant virus than in mice immunized with uninfected cell extract or UV-inactivated wild-type virus. Significantly, latent infection in the trigeminal ganglia was reduced in mice given one immunization with replication-defective mutant virus and was completely prevented by two immunizations. Acute replication in the trigeminal ganglia was also prevented in mice immunized twice with wild-type or mutant virus. The level of protection against infection and disease generated by immunization with replication-defective mutant viruses was comparable to that of infectious wild-type virus in all cases. In addition, T-cell proliferative and neutralizing antibody responses following immunization and corneal challenge were of similar strength in mice immunized with replication-defective mutant viruses or with wild-type virus. Thus, protein expression by forms of HSV-1 capable of only partially completing the replication cycle can induce an immune response in mice that efficiently decreases primary replication of virulent challenge virus, interferes with acute and latent infection of the nervous system, and inhibits the development of both keratitis and systemic neurologic disease.
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FTSNET 0.133 Hrs.
$6.00 Estimated cost this search
$6.00 Estimated total session cost 1.267 DialUnits

File 351:DERWENT WPI 1963-1998/UD=9839;UP=9836;UM=9834
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*File 351: Effective October 1, DialUnit rates adjusted for unrounding.
See HELP NEWS 351 for details.

Set Items Description
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      226 ICP
  1360874 8
        1 ICP(W)8
S3      1 ICP8 OR ICP(W)8
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        0 VMW63
        0 UL54
S4      1 IE63 OR VMW63 OR UL54
       24 IE2
     3258 HERPES?
S5      0 IE2 AND HERPES?
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S6      1 ALPHA(W)27 AND HERPES?
        3 S1
        1 S3
        1 S4
        0 S5
        1 S6
S7      6 S1 OR S3 OR S4 OR S5 OR S6
S8 199143 INJECT?
        6 S7
   199143 S8
S9      1 S7 AND S8
     5488 MUTANT?
     3290 MUTAT?
S10  7276 MUTANT? OR MUTAT?
        6 S7
     7276 S10
S11     2 S7 AND S10
     8917 MOUSE
     7194 MICE
S12 14879 MOUSE OR MICE
        2 S11
    14879 S12
S13     0 S11 AND S12
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Set    Items  Description
S1         3  ICP27 OR ICP(W)27
S2         0  ICP8 O ICP(W)8
S3         1  ICP8 OR ICP(W)8
S4         1  IE63 OR VMW63 OR UL54
S5         0  IE2 AND HERPES?
S6         1  ALPHA(W)27 AND HERPES?
S7         6  S1 OR S3 OR S4 OR S5 OR S6
S8    199143  INJECT?
S9         1  S7 AND S8
S10     7276  MUTANT? OR MUTAT?
S11        2  S7 AND S10
S12    14879  MOUSE OR MICE
S13        0  S11 AND S12
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DIALOG(R)File 351:DERWENT WPI
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011713802
WPI Acc No: 98-130712/199812
XRAM Acc No: C98-043266
 Herpes simplex virus lacking functional ICP34.5 and ICP27 genes - useful
 for, e.g. treating injuries to central nervous system such as Parkinson's
 disease and for gene therapy in mammals
Patent Assignee: MEDICAL RES COUNCIL (MEDI-N)
Inventor: BROWN S M; COFFIN R S; LATCHMAN S D; MACLEAN A R
Number of Countries: 078  Number of Patents: 002
Patent Family:
 Patent No   Kind   Date     Week
 WO 9804726   A1   19980205  199812  B
 AU 9737007   A    19980220  199828
Local Applications (No Type Date): WO 97GB2017 A 19970725; AU 9737007 A
 19970725
Priority Applications (No Type Date): GB 9615794 A 19960726
Abstract (Basic): WO 9804726 A
     A herpes simplex virus (HSV) lacking functional genes ICP34.5 and
   ICP27, is new.
     USE - The HSV strains carrying inactivating mutations in both
   ICP34.5 and ICP27 genes can be used in the preparation of therapeutic
   compositions for treating diseases of, or injuries to, the nervous
   system (claimed), e.g. Parkinson's disease, spinal injury or strokes,
   or diseases of the eye, heart or skeletal muscles, or malignancies. the
   strains can be used for gene therapy in humans and animals (claimed).
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They can also be used for studying the function of genes in mammalian cells (claimed), e.g. identifying genes complementing cellular dysfunctions or studying the effect of expressing mutant genes in wild-type or mutant mammalian cells. The strains may be used in particular for the functional study of genes implicated in disease, e.g. to induce Creutzfeldt-Jakob and other prion-type diseases in the central nervous system of rodents. Other disease models may include those for Alzheimer's disease, motor neuron disease or Parkinson's disease.

ADVANTAGE - The HSV strains carrying both inactivating mutations exhibit greatly improved levels of expression of heterologous genes compared to virus strains carrying mutations in ICP34.5 alone. These doubly-mutated strains are also safer than strains carrying mutations in ICP34.5 alone.

Dwg.0/0

7/27/2
DIALOG(R)File 351:DERWENT WPI
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011446318
WPI Acc No: 97-424225/199739
XRAM Acc No: C97-135707
New herpes simplex virus strains - which are deficient for essential immediate early genes ICP4 and ICP27, used particularly for human gene therapy
Patent Assignee: UNIV PITTSBURGH (UYPI-N)
Inventor: DELUCA N A
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Week	
US 5658724	A	19970819	199739	B

Local Applications (No Type Date): US 92922839 A 19920731; US 94342795 A 19941121
Priority Applications (No Type Date): US 92922839 A 19920731; US 94342795 A 19941121
Abstract (Basic): US 5658724 A

Cell line (A) contains DNA encoding both the herpes simplex virus (HSV) proteins ICP4 and ACP27.

Also claimed are:

(1) an HSV strain whose genome is deficient for the HSV genes encoding ICP4 and ICP27, and

(2) a vector comprising an HSV strain whose genome is deficient for the HSV genes encoding the proteins ICP4 and ICP27, at least 1 exogenous gene to be transferred to a cell, and an appropriate promoter sequence, where the exogenous gene and the promoter sequence are contained within at least 1 non-essential regions of the HSV genome.

USE - The ICP4+ ICP27+ cell lines can be used for producing recombinant HSV strains deficient for both ICP4 and ICP27 which have an extremely low level of wild-type regeneration. They can provide for the expression of a foreign gene from an efficiently delivered HSV genome without cytotoxic side effects. Such strains can be used as vectors, e.g. for human gene therapy or the generation of novel cell lines. In particular they can be used for the mutational inactivation of normal cellular genes or for the repair of mutant cellular genes by homologous recombination.

Dwg.0/4

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